(2,6-diaminopurine), page 13, line 31 (N^2-isobutyrylguanine and $HTEA^+$), page 30, lines 5-12 (phenyl). The amendments focus the scope of the claims on those having antiviral activity for herpes viruses and their synthetic intermediates.

Rejection under 35 U.S.C. § 112, first paragraph

The Office objected to the specification and rejected claims 7, 10 and 27 as allegedly not supported by an enabling disclosure. The Office asserted that the specification provided no guidance with regard to which viruses the claimed compounds might have activity against.

Applicants direct the Office's attention to page 6, lines 16-29 which indicate that the claimed compounds have activity against, for example, herpes viruses. Applicants believe that in view of the disclosure and the state of the art in which one of ordinary skill in the art would know that herpes viruses would be suitable agents for the compounds. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. §103

The Office rejected claims 7, 10 and 27 as allegedly prima facie obvious over either Borthwick et al (*J. Med. Chem.* 34:907-914, 1991) or Chu et al (*Chem. Pharm. Bull.* 37:336-339, 1989, of record) in view of Reist et al (WO84/04748, of record). The references are of record. The Office asserted that the primary references disclosed "unphosphorylated nucleoside of claim 27" and that Reist teaches the "5'-phosphonate derivatives of the known antiviral nucleoside analogs.

Applicants pointed out in amendment B, filed December 15, 1993, that in establishing prima facie obviousness, the Office must show some objective teaching in the cited references that would lead an individual to combine the relevant teachings as evidence of obviousness. *In re Lalu* 223 U.S.P.Q. 1257 (Fed. Cir. 1987). Both the suggestion and the expectation of success must be founded in the cited art, not in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Hindsight reconstruction using applicant's disclosure and claims cannot be used as a guide to pick and choose among isolated elements to arrive at the claimed invention. *In re Fine* 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). In determining the scope and content of the cited art, the references must be considered in their entirety, as a whole, including portions that lead away from the claimed invention. *In re*

Panduit 1 U.S.P.Q. 2d 1593 (Fed. Cir. 1987). A reference cited in support of a rejection under section 103 is not properly relied upon if the reference is from a field of endeavor that is different from the inventor's field and if the reference is not reasonably pertinent to the particular problem with which the inventor is involved. *In re Clay* 23 U.S.P.Q. 2d 1058 (Fed. Cir. 1992), *In re Deminski* 230 U.S.P.Q. 313 (Fed. Cir. 1986), 796 F.2d 436, 442. The purposes of both the invention and the cited reference are important in determining whether the reference is reasonably pertinent to the problem the invention attempts to solve. In making a determination that a reference is properly cited, the similarities and differences in structure and function between the reference and the claimed invention must be considered. *In re Clay*, supra; *In re Ellis* 177 U.S.P.Q. 526, 527 (C.C.P.A. 1973).

Applicants note that the Borthwick publication has a publication date that is later than Applicant's filing date. Borthwick was published in the March 1991 issue of *J. Med. Chem.*, while Applicant's filing date is February 8, 1991. Because of its later publication date, the Borthwick publication is improperly applied in this case. A copy of the Borthwick study and the table of contents showing the publication date is attached.

The present rejection is similar to the rejection issued by the Office in the Office action dated August 9, 1993, except that the present rejection now uses Chu in place of the secondary reference by Montgomery et al (*J. Med. Chem.* 22:109 1979, of record, hereafter Montgomery). Montgomery taught that replacing the 5' phosphate group of 2'-deoxy-5-fluorouridylic acid with a 5' phosphonate group did not yield a molecule with the same biological properties of the parent molecule. Applicants appreciate the omission of Montgomery from the present rejection. Applicants argued in amendment B that this reference taught away from applicant's claimed compounds. The Office accepted this argument by removing Montgomery from the rejection. Because Montgomery taught away from the presently claimed compounds, The Office is obliged to consider this teaching in evaluating the patentability of the claimed compositions and cannot ignore it by removing Montgomery from the rejection. *In re Panduit*, supra. Applicants respectfully request reconsideration and withdrawal of the rejection in view of the teaching of Montgomery.

Turning to Chu, he states at page 337, second column, paragraph bridging to page 338

> "None of the new 2'-F-ara-purines demonstrated significant antiviral activity against HSV-1."

Chu thus teaches away from Applicant's claimed invention. The Office asserted that compound VI in Table II at page 338 was an effective antiviral agent. However, the data in Table II was demonstrated cytotoxicity toward tumor cells and not any antiviral activity. The Table II data did not include any cytotoxicity toward normal cells, and the cell killing was apparently due primarily to nonspecific cytotoxicity where Chu stated at page 337, second column "2'-F-ara-G (IV) is more toxic in mice (ID_{50} = 125 mg/kg x 10d) than the thioguanine analog (ID_{50} = 400 mg/kg). Further antileukemic evaluation is now in progress." Chu teaches that the 2'-deoxy-2'-fluoroarabinofuranosyl purine compounds are inactive as antiviral agents but do have significant cytotoxicity toward cells. This study would have led one to conclude this class of compounds was not suitable as candidates for antiviral agents and provided no objective basis for an expectation of success by making phosphonates thereof to improve the situation.

The Office's attention is directed to a publication by some of the coinventors of the present application, Buhr et al (*Collect. Czech. Chem. Commun.* 58:102-104 1993, newly cited) which describes the activity of 5'-methylene phosphonate compounds as inhibitors of several herpes viruses. The results show that the compounds are very sensitive to structural modifications and the resulting antiviral activity is not predictable, which one would expect from Montgomery as discussed above. Compounds with antiviral activity at the tested levels were the 5' methylene phosphonate analogs of 2'-deoxyguanosine and 2'-deoxy-2'-arafluoroguanosine, which the amended claims now recite.

Applicants respectfully request reconsideration and withdrawal of the rejection.

This application is now believed to be in condition for allowance. Applicants solicit an early Notice to that effect.

Respectfully submitted,

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